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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/009,809
Filing Date: April 26, 2002
Appellant(s): EISENBERG ET AL.

Kenneth A. Weber
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 07/20/2009 appealing from the Office action mailed 01/05/2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

On page 3 of the Appeal Brief filed on July 20, 2009, appellant identifies related US Patent 7,112,568 and USSNs 11/495,625 and 11/214,588.

For US Patent 7,112,568, a terminal disclaimer was filed on June 10, 2008 and was approved on July 11, 2008.

For USSN 11/214,588, a terminal disclaimer was filed on February 11, 2009 and was approved on March 17, 2009.

USSN 11/495,625 has been expressly abandoned on March 5, 2009.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner for following reasons.

In view of the abandonment of copending USSN 11/495,625, the prior provisional obviousness-type double patenting rejection over claims 1-24 of copending USSN 11/495,625, set forth on page 5 of the Office Action mailed on January 5, 2009, has been rendered moot.

In view of the Terminal Disclaimer, filed on February 11, 2009, the previous nonstatutory obviousness-type double patenting rejection over claims 1 and 3-15 of copending USSN 11/214,588 (see pages 5-6 of the Office Action mailed on January 5, 2009) has been withdrawn.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Holgate et al. "The mast cell", British Medical Bulletin, vol. 48, no.1 (1992), pp. 40-50.

Adridor et al. "Activation of Exocytosis by the Heterotrimeric G Protein Gi3", Science, vol. 262 (1993), pp. 1569-1572.

Jackson et al. "Template-Constrained Cyclic Peptides: Design of High-Affinity Ligands for GPIIb/IIa", J. Am. Chem. Soc., vol. 116, (1994), pp. 3220-3230.

Lin et al., US Patent 5,807,746, September 15, 1998.

Avruch et al., US Patent 6,103,692, August 15, 2000.

(9) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

Rejections under 35 U.S.C. 103(a)

A) Claims 63, 66-70, and 72-78 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Holgate et al. (British Medical Bulletin. 1992. 48;1:40-50, see entire document) in view of Adridor et al. (Science 1993. 262:1569-1572, see entire document) and Lin et al. (US Patent 5,807,746, see entire document) for the reasons of record.

Holgate et al. teach that mast cell degranulation has been associated with the development of asthma, and pharmacological agents that can suppress the release of mast cell mediators have been shown to be clinically effective in treating asthma (see entire document, particularly lines 9-20 on page 47 under "MAST CELLS IN CLINICAL ASTHMA").

The reference teachings differ from the claimed invention by not describing a complex peptide with a first segment having the amino acid sequence of AAVALLPAVLLALLAP (SEQ ID NO:3) linked to a second segment having the amino acid sequence of KNNLKECGLY (SEQ ID NO:1).

However, the role of the claimed second segment having the amino acid sequence of KNNLKECGLY in inhibiting mast cell degranulation was well know in the art at the time of the invention. For example, Adridor et al. teach that the synthetic peptide KNNLKECGLY (also called EC peptide by Adridor et al. (see reference 21 on page 1571, same amino acid sequence as the instant SEQ ID NO:1), corresponding to the C-terminal end of protein $G\alpha_{i3}$, inhibits permeabilzed mast cell degranulation (see entire document, particularly lines 16-19 of the second full paragraph on the left column and Figure 2 on page 1570). Adridor et al. further teach that peptide KNNLKECGLY was ineffective when added to intact cells indicating that the target for the peptide was intracellular (e.g. see lines 1-3 on the right column on page 1570).

The use of peptides for importing biologically active molecules into cells was also well known in the art at the time of the invention. Lin et al. teach a peptide with the amino acid sequence of AAVALLPAVLLALLAP (SEQ ID NO: 5 in Lin et al., same amino acid sequence as the instant SEQ ID NO:3), derived from Kaposi fibroblast growth factor, is a useful signal peptide that is capable of translocating biologically active molecules across the cell membrane (e.g. see first full paragraph on column 7). Lin et al. further provides working examples of the signal peptide AAVALLPAVLLALLAP linked to biologically active peptides via peptide bonds and show that the signal peptide is capable of transporting biologically active peptides across the cell membrane and once inside the cell, the biologically active peptides retain their function (e.g. Examples on columns 11-17).

Furthermore, Lin et al. teach that the importation is based upon mechanisms naturally occurring in cells thus avoiding damaging the target cells, and can be used to import molecules into large numbers of cells including organs providing treatments of diseases (e.g. see lines 17-25 of the first full paragraph on column 2).

It would thus have been obvious to the ordinary artisan at the time the invention was made to develop methods of inhibiting mast cell degranulation using the synthetic peptide KNNLKECGLY linked to an importation competent signal peptide AAVALLPAVLLALLAP for intracellular delivery. The ordinary artisan would have been motivated to do so because mast cell degranulation was associated with asthma, and pharmacological agents that can suppress the release of mast cell mediators have been shown to be clinically effective, and the intracellularly targeting synthetic peptide KNNLKECGLY was a well known agent in inhibiting mast cell degranulation, and the importation competent signal peptide AAVALLPAVLLALLAP could be linked to peptides to facilitate delivery of peptides into cells using naturally occurring mechanisms.

Given the teachings of Holgate et al regarding the role of mast cell degranulation in asthma, and the teachings of Adridor et al. and Lin et al. providing the method of inhibiting mast cell degranulation by synthetic peptide KNNLKECGLY and methods of delivering biological

molecule into cell by using the importation competent signal peptide AAVALLPAVLLALLAP, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success in producing the claimed methods.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

B) Claims 64 and 65 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Holgate et al. (British Medical Bulletin. 1992. 48;1:40-50) in view of Adridor et al. (Science 1993. 262:1569-1572) and Lin et al. (US Patent 5,807,746) as applied to claim 63 above, further in view of Avruch et al. (US Patent 6,103,692) and Jackson et al. (J. Am. Chem. Soc. 1994. 116:3220-3230) for the reasons of record.

The teachings of Holgate et al, Adridor et al, and Lin et al have been discussed, supra.

The reference teachings differ from the claimed invention by not describing cyclization and succinyl residue at the N terminus of the peptide.

However, methods of modifying peptides for improved efficiency were well known in the art at the time the invention was made. For example, Avruch et al. teach that adding amino-terminal blocking groups, e.g. succinyl group, to a peptide is beneficial in that succinylation increases the peptide's passage through the hydrophobic cellular membrane (see entire document, particularly paragraph spanning columns 12 and 13). Jackson et al. teach cyclization of peptides is a highly successful strategy for restricting the conformation of peptides and can give rise to impressive gains in affinity, receptor subtype specificity and restriction of conformational mobility (see entire document, particularly lines 5-10 on the right column on page 3220).

It would thus have been obvious to an ordinary artisan at the time the invention was made to modify the biologically active peptides by cyclization and succynylation for advantages including increased passage through cell membrane, enhanced affinity, receptor subtype specificity and restriction of conformational mobility. The ordinary artisan would have been motivated to modify the claimed peptide for the use in inhibiting mast cell degranulation.

Given the teachings of Holgate et al, Adridor et al, and Lin et al, regarding the role of the peptide in inhibiting mast cell degranulation, and the teachings of Avruch et al and Jackson et al, providing the advantages of peptide modifications such as cyclization and succinylation, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

A) Response to argument to rejection under 35 U.S.C. 103(a) against claims 63, 66-70, and 72-78 based upon Holgate et al. (British Medical Bulletin. 1992. 48;1:40-50), Adridor et al. (Science 1993. 262:1569-1572) and Lin et al. (US Patent 5,807,746).

The claims are drawn to a method of inhibiting mast cell degranulation in a subject by administering a therapeutic agent comprising a first segment having amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 3, also called signal peptide in the prior art and cell penetrating peptide (CELL PENETRATING PEPTIDE) by appellant) linked via a linker to a second segment having an amino acid sequence KNNLKECGLY (SEQ ID NO: 1, also called mast cell inhibitor by appellant).

Appellant's arguments in conjunction with the two declarations by Razin and the Sagi-Eisenberg, under 37 CFR 1.132, filed on June 28, 2007 have been fully considered but have not been found persuasive.

Appellant's arguments, the two declarations under 37 CFR 1.132, and the Examiner's rebuttal are essentially the same of record.

Appellant in conjunction with the Razin and the Sagi-Eisenberg declarations asserts that it is unpredictable whether the biological activity of the mast cell degranulation inhibiting peptides would be retained once said peptides are linked to the cell penetrating peptide. Specifically, based on appellant's own work and the evidence provided in the two declarations, appellant asserts that only the cell penetrating peptide AAVALLPAVLLALLAP fused peptides retain biological activity; the other cell penetrating peptides are not able to retain the inhibitory activity (inhibiting mast cell degranulation) of the peptides they transport. In the Table on page 7 of the Brief, appellant provides examples of following four different cell penetrating peptides:

human integrin β3 (Hu Int),
Kaposi fibroblast growth factor (KFGF) (AAVALLPAVLLALLAP),
Drosophila transcription factor (Dros), and
tanspotan 10 (TP-10)

fused to two different mast cell inhibiting peptides $G_{\alpha i3}$ and $G_{\alpha t}$ and asserts that only the cell penetrating peptide with the claimed sequence of AAVALLPAVLLALLAP is able to both internalize and maintain the inhibitory activity of the peptides $G_{\alpha i3}$ and $G_{\alpha t}$; the other cell penetrating peptides, Hu Int, Dros, and TP-10, are not able to retain the inhibitory activity of the peptides $G_{\alpha i3}$ and $G_{\alpha t}$. Thus, Appellant asserts that it is unpredictable whether mast cell inhibitor peptides once fused to penetrating peptides will be able to retain the biological effect of the mast cell inhibiting peptides. Appellant asserts that factors explaining this unpredictability include conformation changes associated with the fusion, degradation of protein in mast cells, location of

the peptide in an endosome, or inability of the cell penetrating peptides to trigger mast degranulation.

Appellant's arguments of unpredictability are not found persuasive for the following reasons:

The prior art of Lin et al. as well as appellant's own evidence consistently teach that the claimed peptide AAVALLPAVLLALLAP (SEQ ID NO: 3) is capable of not only transporting various peptides across cell membranes of different cell types, but is also able to retain the biological activities of the peptide it transports. **There is no evidence, either in prior art or the instant specification, showing that AAVALLPAVLLALLAP (KFGF) does not work.**

In *KSR,* the Supreme Court indicated that "[w]hen a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *KSR Int'l v. Teleflex Inc.,* 127 S. Ct. 1727, 1740 (2007).

In this case, Lin et al. (US Patent 5,807,746) teach that it is routine to test signal peptides for their ability to translocate across the cell membrane of any given cell type and that the signal peptide can be conjugated to a biologically active molecule, administered to a cell and the cell is subsequently screened for the presence of the active molecule and its biological function (see entire document, particularly lines 57-65 on column 6). Lin et al. further provide working examples of AAVALLPAVLLALLAP (KFGF) linked to several biological peptides including the nuclear localization sequence of acidic FGF (e.g. see lines 11-15 of the second full paragraph on column 15) and functional domain of the nuclear factor kB (see columns 16-17 in particular). Lin et al. states on lines 11-15 of the second full paragraph on column 15:

> *"SA peptide therefore was effective in mitogenesis because it contained both the signal peptide sequence of K-FGF (for import into the cell) and nuclear localization sequence of aFGF (for mitogenic activity)."*

Lin et al. tested a fusion, SN50, containing AAVALLPAVLLALLAP (KFGF) and a biologically active peptide N50 (the nuclear localization sequence (NLS) of the nuclear factor κB (NF- κB) p50 subunit)and show SN50 can inhibit nuclear translocation of the NF- κB, indicating AAVALLPAVLLALLAP not only transports N50 across cell membrane but also retains the inhibitory effect of the N50 peptide (e.g. see columns 16-17, particularly lines 36-42 of column 17 or see copy below)

> *"These results suggest that neither the hydrophobic sequence alone (SM peptide) nor the nuclear localization sequence alone (N50 peptide) was sufficient for causing a functional inhibition of the NF-kappa.B. Therefore, the observed inhibitory effect of SN50 must be attributed to its intracellular import, which allowed the interaction of its intrinsic NLS with the nuclear membranes.*

The KFGF peptide AAVALLPAVLLALLAP (instant SEQ ID NO:3) is capable of not only importing signal sequence-containing peptides but also maintaining the functions of the transported peptides.

Additionally, Lin et al. teach that AAVALLPAVLLALLAP fused biologically active peptides can be administered to a subject for treatment of diseases (e.g. see paragraphs spanning columns 8-10).

Consistent with the teachings of the prior art, appellant's own evidence shows that KFGF peptide AAVALLPAVLLALLAP is able to deliver two mast cell inhibitory peptides Gαi3 and Gαt across cell membrane and the inhibitory peptides retain their biological function inside mast cells (e.g. see KFGF on rows 2 and 5 of the table on page 7 of the Brief).

Therefore, the claimed cell penetrating peptide AAVALLPAVLLALLAP (instant SEQ ID NO:3) has been shown to be able to transport four different cargo peptides including Gαi3 and Gαt (both disclosed in the instant specification), nuclear localization sequence of acidic FGF (see columns 14-15 in Lin et al) and functional domain of the nuclear factor kB (see columns 16-17 of Lin et al) and maintain their biological activities.

Thus, the use of AAVALLPAVLLALLAP (instant SEQ ID NO:3) to transport inhibitory peptide KNNLKECGLY (instant SEQ ID NO:1) across mast cell membranes represents a predictable approach that the ordinary practitioner would apply to obtain a therapeutic agent to the method taught by Holgate et al. (administering pharmaceutical agents that suppress the release of mast cell mediators for treating asthma). Such a combination is merely a "predictable use of prior art elements according to their established functions." *KSR*, 127 S. Ct. at 1740.

Appellant's arguments relying on other cell penetrating peptides including human integrin β3 (Hu Int), Drosophila transcription factor (Dros), and tanspotan 10 (TP-10) to show unpredictability and surprising results have not been found persuasive because those cell penetrating peptides are not being claimed, nor relied upon by the prior art.

On page 5 of the Brief (filed on 07/20/2009) under TECHNICAL OVERVIEW, appellant asserts that both Examiners Nolan and Crowder (currently Dahle) support the view that the filed of cell penetrating peptide (CPP) is unpredictable in their previous rejections under 35 U.S.C. 112, first paragraph, enablement. It is noted that Examiner Nolan states clearly that the use of the AAVALLPAVLLALLAP peptide is enabled (see page 4 of the non-final Office Action mailed on April 8, 2005). The enablement rejection by Examiner Nolan is towards the claims mailed on January 18, 2005 (see copy below):

"Claim 44 (Currently Amended) A method for treating an allergic condition in a subject, comprising administering a pharmaceutically effective amount of a therapeutic agent to the subject, said therapeutic agent comprising a molecule having at least a first segment competent for importation of said molecule into mast cells in vivo, and a second segment for having an anti-allergic effect within said mast cells, said first segment being joined to said second segment through a linker, whereby the complex molecule is capable of exerting its anti-allergic effect in vivo ~~The method of claim 30,~~ and wherein said second segment is a peptide taken from the C terminal sequence of $G_{\alpha i}$."

While the use of AAVALLPAVLLALLAP is enabled, the use of any importation peptides to treat allergies is not.

Examiner Crowder rejected the claims under 35 U.S.C. 112, first paragraph, enablement for the prior recited limitation of "preventing mast cell degranulation in a subject" (e.g. see page 4 of the Office Action mailed on August 2, 2006 and see claim filed May 1, 2006 or see copy below).

"44. (Currently Amended) A method of preventing mast cell ~~degranulation treating an allergic condition~~ in a subject, the method comprising administering to the subject a pharmaceutically effective amount of a ~~therapeutic agent to~~ the subject, ~~said~~ therapeutic agent wherein said therapeutic agent ~~comprising~~ comprises a complex molecule which comprises ~~having at least a fi~t segment~ompotont for importation of ~aid molecule-into mast oolio i~,h,o, and a-~ooondcegment for haxdng an anti allergic effect within said mast cells, said first segment being joined to said second segment through a linker, whereby the complex moleoule is capable of~ exerting ~its anti allergic effect in vivo, wherein said complex molecule is a peptide having aria~ a first segment having an amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO:3) linked via a linker to a second segment having an amino acid sequence KENLKDCGLF (SEQ ID NO:2) preventing mast cell degranulation in the subject"

While preventing method is not enabled, the method of inhibiting mast cell degranulation by using the claimed peptides is.

Both rejections have been with drawn after appellant amended the claims.

Therefore, the examiner's position has been consistent throughout the prosecution that the use of AAVALLPAVLLALLAP (instant SEQ ID NO:3) to transport inhibitory peptide KNNLKECGLY (instant SEQ ID NO:1) across mast cell membranes represents a predictable approach that the ordinary practitioner would apply to obtain a therapeutic agent to the method taught by Holgate et al. (administering pharmaceutical agents that suppress the release of mast cell mediators for treating asthma).

Appellant has not provided objective evidence to show that AAVALLPAVLLALLAP is unpredictable in transporting and maintaining function of biological peptides.

Further, appellant argues that since AAVALLPAVLLALLAP has not been shown to be superior over other cell penetrating peptides in the prior art, the data showing that only AAVALLPAVLLALLAP works in retaining the inhibitory effect of $G_{\alpha i3}$ and $G_{\alpha t}$ but not the other known transporting peptides including Hu Int, Dros, and TP-10 is a surprising result, sufficient to demonstrate the claimed invention is non-obvious.

This is not found persuasive for the following reasons:

As demonstrated by the prior art, concerns raised by the Razin and Sagi-Eisenberg declarations represent issues of which the ordinary practitioner would have been aware and consequently the use of Lin et al.'s cell penetrating peptide AAVALLPAVLLALLAP (importing biologically active molecule into a cell using mechanisms naturally occurring in cells, e.g. see lines 17-25 of the first full paragraph of column 2 of Lin et al.) to deliver inhibitory KNNLKECGLY (targeting intracellularly, e.g. see lines 1-3 of the last paragraph of the right column on page 1570 of Aridor et al.) so that the inhibitory peptide maintains functional inside mast cell is the expected and unsurprising result.

Aridor et al. provide clear motivation to one of skill in the art to transport inhibitory peptide into mast cells since the peptide only inhibits mast cell degranulation intracellularly. One of ordinary skill in the art would have been motivated to make a fusion protein comprising AAVALLPAVLLALLAP taught by Lin et al. with the inhibitory peptide, with a reasonable expectation of success. The results of the fusion peptide can be easily tested for the function of mast cell inhibition using methodology taught by Aridor et al. Thus, it is predictable and unsurprising that the two peptides linked together can be transported across mast cell membrane and fully functional in inhibiting mast cell degranulation.

Given that the claimed cell penetrating peptide AAVALLPAVLLALLAP (instant SEQ ID NO:3) and the mast cell inhibitory cargo peptide KNNLKECGLY (instant SEQ ID NO:1) have the identical sequences as the prior art peptides taught by Lin et al. and Adridor et al, respectively, and these two peptides can be linked via the same linker as taught by the Lin et al,

it is predictable and expected that AAVALLPAVLLALLAP (instant SEQ ID NO:3) would be able to transport peptides such as KNNLKECGLY (instant SEQ ID NO:1) and retain their biological activities including inhibitory effect on mast cell degranulation.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according to known methods to yield predictable results.

The rationale to support a conclusion that the claims would have been obvious is that all the claimed elements (methods of inhibiting mast cell degranulation for treating asthma, the cell penetrating peptide AAVALLPAVLLALLAP, and inhibitory peptide KNNLKECGLY) were known in the prior art and one skilled in the art would have been prompted to combine the elements in the way the claimed invention does by linking the cell penetrating peptide to the inhibitory peptide via a linker and administering the fusion peptide to a subject with asthma, and the combination would have yielded nothing more than predictable results of a method of inhibiting mast cell degranulation in a subject by administering the fusion peptide.

The nature of the problem to be solved --- delivering mast cell inhibitory peptide across the mast cell membrane ----- as well as the need to inhibit mast cell degranulation in treating asthma, would have lead one of ordinary skill in the art to choose an appropriate cell penetrating peptide. Therefore, it would have been obvious to use the cell penetrating peptide as shown in Lin et al. in combination with the inhibitory peptide (as taught by Arido et al.) to inhibit mast cell degranulation in a subject suffering from asthma.

B) Simple substitution of one known element for another to obtain predictable results.

The rationale to support a conclusion that the claims would have been obvious is that the substitution of one known element that is linked to AAVALLPAVLLALLAP (e.g. known biological active peptides aFGF and N50 taught by Lin et al.) with another (KNNLKECGLY capable of inhibiting mast cell degranulation once transported inside cells as taught by Aridor et al.) would have yielded predictable results of a fusion peptide comprising both AAVALLPAVLLALLAP and KNNLKECGLY that can be used in a method of inhibiting mast cell degranulation in asthma patients . Because Holgate et al. teach that mast cell degranulation has been associated with the development of asthma, and pharmacological agents that can suppress the release of mast cell mediators can treat asthma (see entire document, particularly lines 9-20 on page 47 under "MAST CELLS IN CLINICAL ASTHMA", Aridor et al. teach KNNLKECGLY can inhibit mast cell degranulation once it has penetrated the cell membrane, Lin et al. teach AAVALLPAVLLALLAP is able to lead other biological active peptides across cell membrane and retain their function), it would be *prima facie* obvious to substitute pharmacological agents taught by Holgate et al. with AAVALLPAVLLALLAP and KNNLKECGLY.

C) Use of known technique to improve similar products/methods in the same way.

The rationale to support a conclusion that the claims would have been obvious is that a method of enhancing the effect of biologically active peptides by linking them to the cell penetrating peptide AAVALLPAVLLALLAP was made part of ordinary capabilities of one skilled in the art based upon the teachings of Lin et al. One of ordinary skill in the art would have been capable of applying this method to a known mast cell inhibiting peptide KNNLKECGLY taught by Aridor et al. so that the inhibiting peptide can penetrate the mast cell membrane to inhibit mast cell degranulation, and the results would have been predictable to one of ordinary skill in the art.

D) Applying a known technique to a known product/method ready for improvement to yield predictable results.

The rationale to support a conclusion that the claims would have been obvious is that a particular known method of treating asthma by administering agents that can inhibit mast cell degranulation was recognized as part of the ordinary capabilities of one skilled in the art, so was the use of AAVALLPAVLLALLAP for delivering biological active peptides (e.g. mast cell inhibitory peptide KNNLKECGLY) across the cell membrane their targets. One of ordinary skill in the art would have been capable of applying the known methods to a known product of KNNLKECGLY and known method of treating asthma that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

The basic technique of linking cell penetrating peptide to biologically active peptides which then enable biologically active peptides to reach their intracellular targets would have yielded no more than the predictable outcome of a fusion peptide (comprising AAVALLPAVLLALLAP and KNNLKECGLY), capable of penetrating mast cell membrane and maintaining a biological function, that can be used in a method of inhibiting mast cell degranulation in a subject.

E) "Obvious to try" --- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

The rationale to support a conclusion that the claims would have been obvious is that a person of ordinary skill has good reason to pursue the known options (linking mast cell inhibiting peptide KNNLKECGLY to cell penetrating peptide AAVALLPAVLLALLAP and use the fusion peptide for the method of inhibiting mast cell degranulation to treat asthma) within his or her technical grasp. The claims were obvious because it would have been obvious to try the known methods of linking the two claimed peptides via a linker and use the linked peptide for an in vivo method of inhibiting mast cell degranulation, with a reasonable expectation of success.

The prior art Lin et al. had taught a complex comprising the molecule linked to a signal peptide capable of delivering biologically active peptides into the interior of cells, as exemplified

by AAVALLPAVLLALLAP comprising complex. Aridor et al. had identified KNNLKECGLY that targets intracellularly in mast cells to inhibit mast cell degranulation. Finally, Holgate et al. has taught a generally applicable method for treating asthma patients by administering pharmaceutical agents that can inhibit mast cell degranulation. The prior art had recognized the obstacles to be overcome in the development of therapeutic peptides, mainly delivery of said peptides into a cell and had suggested a finite number of cell penetrating peptides (e.g. AAVALLPAVLLALLAP) to overcome these obstacles. The claims were obvious because it would have been obvious to try the known methods for delivering therapeutic peptides across cell membrane relying upon cell penetrating peptide, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would have lead one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

The teachings of Aridor et al. pertaining to the biological effect of the peptide KNNLKECGLY in inhibiting mast cell degranulation for targeting intracellular targets and the teachings of Lin et al. indicating success in importing biologically active molecules into cell by linking cell-penetrating peptides (e.g. AAVALLPAVLLALLAP) to the biological molecules via linkers would have motivated one of ordinary skill in the art at the time the invention was made to combine the references to arrive at the claimed invention of method of inhibiting mast cell degranulation using a complex molecule comprising cell-penetrating peptide AAVALLPAVLLALLAP linked via a linker to the biologically active peptide KNNLKECGLY capable of inhibiting mast cell degranulation.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Here, given that the prior art goal was to treat asthma by inhibiting mast cell degranulation and the prior art KNNLKECGLY is capable of fulfilling such goal once it gets inside mast cell, incorporating the well-known AAVALLPAVLLALLAP to facilitate the transport of KNNLKECGLY across mast cell membranes would have been obvious to the ordinary artisan at the time of the invention.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

B) Response to argument to rejection under 35 U.S.C. 103(a) against claims 64 and 65 based upon Holgate et al. (British Medical Bulletin. 1992. 48;1:40-50), Adridor et al. (Science 1993. 262:1569-1572), Lin et al. (US Patent 5,807,746), Avruch et al. (US Patent 6,103,692) and Jackson et al. (J. Am. Chem. Soc. 1994. 116:3220-3230).

Appellant's arguments and the Examiner's rebuttal regarding the teachings of Holgate et al. (British Medical Bulletin. 1992. 48;1:40-50), Adridor et al. (Science 1993. 262:1569-1572), and Lin et al. (US Patent 5,807,746) are essentially the same as discussed, supra.

Given that the independent claim 63 is rejected (see detailed discussion above), the dependent claims 64 and 65 stands rejected for the reasons of record.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,
Chun Dahle
Patent Examiner

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